The Treatment of Inoperable Malignant Tumors with the Toxins of Erysipelas and Bacillus Prodigiosus

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BY

WILLIAM B. COLEY, M.D.

ATTENDING SURGEON TO THE NEW YORK CANCER HOSPITAL; ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED

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THE TREATMENT OF INOPERABLE MALIGNANT TUMORS WITH THE TOXINS OF ERYSIPELAS AND BACILLUS PRODIGIOSUS.[1]

I AM conscious that the treatment of inoperable tumors is a very trite subject, yet in consideration of the fact that practically no advance has been made in this field since the disease was first known, I am sure I need offer no apology if I can show that there has been even a single step forward. No one can blame the profession for sound conservatism, or even scepticism, in regard to anything that is claimed to cure inoperable malignant tumors. Past experience fully justifies its attitude, and I believe it should not accept a single statement until it has stood the rigid tests of scientific demonstration. By these tests alone I desire you to judge the cases I have already reported, as well as those I have the pleasure of presenting to-night. My results in thirty-five cases of inoperable tumors treated with the toxins during the past three years, were reported in detail at the last meeting of the American Surgical Association,[2] at Washington, May 31, 1894, and will be only briefly referred to here.

Four very remarkable successes since then, and the additional experience gained from the observation of twenty-four new cases, are, I think, sufficient reasons for bringing this subject again to your attention.

Up to last May my cases were treated with the filtered toxins, prepared by growing the erysipelas streptococci in bouillon three weeks, then filtering through porcelain, and preserving by adding thymol. The toxins of bacillus prodigiosus were prepared in the same

[1] Read at the General Meeting of the Academy of Medicine, November 15, 1894.

[2] American Journal of the Medical Sciences, July, 1894.

way, and the two were mixed at the time of using. In some of the cases the two germs were grown together in the same flasks, and then filtered. This method of preparation failed to utilize whatever of value exists in the bodies of the germs themselves, and I decided to try preparing the toxins by subjecting the cultures to the lowest temperature that would suffice to destroy the germs. This I found by experiment to be about 58° C. This preparation has been used exclusively in the series of twenty-four cases which I report to-night, and it is, I think, much more efficacious than the filtered toxins.

The following is a brief history of the more important cases treated since June 1, 1894, and not yet reported :

Case I.—Female, twenty years of age. Recurrent spindle-celled sarcoma of palm of hand ; six operations. This case appears in the tables of my previous paper (*loc. cit.*) as Case VI., and is merely mentioned as having shown marked improvement, and as being still "under treatment." The subsequent history makes the case worthy of a fuller report.

The first operation was performed in the fall of 1888. The tumor did not recur until the summer of 1891. A second operation was performed and recurrence again followed ; the third, fourth, and fifth operations were performed, recurrence each time occurring after shorter intervals.

The fifth operation was performed in January, 1893, by Dr. Samuel Lloyd, of New York, and recurrence followed within three weeks. I saw the patient, in consultation with Dr. Lloyd, in February, 1893, and at that time a tumor, the size of half a hen's egg, was seen in the palm of the right hand at the site of the old cicatrices. It was a typical sarcoma clinically, and the diagnosis had been repeatedly confirmed by microscopical examination. Amputation of the forearm had been very strongly urged, but the patient refused consent to such operation. The axillary glands were slightly

enlarged, her general condition was only fair. Injections with the mixed toxins were begun under my direction, and often by myself personally, and the treatment was continued by Dr. Lloyd, with longer or shorter intervals, during the whole spring. The tumor decreased some in size and failed to grow when the injections were stopped for a short time. She had little treatment during the summer, and in October, 1893, the axillary glands were very much enlarged. The tumor in the hand was also beginning to increase in size. Dr. Lloyd operated upon the axilla and removed several glands, some of which were as large as large olives, and typically sarcomatous. The tumor of the hand was then treated with the injections of the mixed toxins.

The patient was unable to remain in a hospital, and the injections were given at Dr. Lloyd's office. This made it impossible to push the injections to the desired limit, and made the treatment otherwise unsatisfactory. Whenever the injections were given regularly and in fairly large doses the tumor remained in control, and furthermore decreased in size.

In June, 1894, she was admitted to my service at the New York Cancer Hospital, and the injections were pushed to their limit for about three weeks. The tumor softened and also decreased some in size. As the patient's general condition had been running down for several months, I thought it wise to give ether and scrape out the more or less necrotic sarcomatous tissue. It was found to extend very deeply, entirely surrounding the palmar tendons of the middle, ring, and little fingers, and infiltrating between the metacarpal bones so as almost to appear on the dorsal side. It was removed as well as possible with a Volkmann spoon and scissors, and the extensive wound allowed to heal by granulation ; no further injections were given. She quickly began to improve in health, and has now regained her normal weight and strength. She has gained twenty pounds since July. No trace of any trouble can be de-

tected either in the hand or axilla. This case is important, as it shows that a rapidly growing sarcoma was held in check one year and a half by the toxins, even when given under unfavorable conditions, and also that the malignancy of the disease was probably destroyed.[1]

Case II.—This case I owe to the courtesy of Dr. George F. Shrady, who kindly asked me to begin the treatment at St. Francis Hospital. Bernard M——, aged twenty-three, German, printer by occupation. His family history is good, and up to one year ago he had enjoyed perfect health. Ten years ago he fell from a fourth-story window, but was supposed to have suffered no permanent injury. Three years ago he fell in the streets, striking upon his back. He, however, noticed no trouble from either of these injuries, until one year ago a tumor appeared in his back, in the region of the right buttock. There was little pain, and his attention was first called to it by the fact that he was unable to button his trousers. The tumor was hard, apparently rising from the ilium, and gradually extended until it had involved nearly the entire right half of the ilium. In February, 1894, it had reached the size of a child's head, and extended from the middle of the sacrum behind nearly to the edge of the rectus muscle in front, filling up a large portion of the right iliac fossa. The tumor was firm in consistence, the skin over it normal, and not adherent. The right inguinal glands were very much enlarged. The patient was considerably emaciated, and was losing flesh and strength rapidly. He was shown at the New York Academy of Medicine by Dr. Kammerer, in February, 1894, before the Surgical Section, and the question as to the advisability of subjecting him to the treatment with erysipelas and prodigiosus toxins was discussed. The weight of opinion was that the tumor was too large and the case too far advanced to offer even a hope of success. It was

[1] The case remains in perfect health January 1, 1895, nearly six months since cessation of treatment.

thought best, however, to try the injections for a brief time, and the treatment was begun at St. Francis Hospital in March 1894. Injections were continued at intervals of twenty-four to forty-eight hours for a period of one month. The tumor very quickly began to break down, and fluctuation appeared over a large area. Free incision and irrigation were employed, and the tumor continued to break down and slough out in large masses for a number of weeks after the injections were stopped. The patient was considerably depressed both by the treatment and by the sloughing process, and for some weeks his condition was exceedingly critical. His temperature ran very high for a month after the injections had been stopped, due to the absorption of the broken-down tissue. As the discharge began to diminish, his condition improved, and by June he was able to be up and about the ward. Since that time he has steadily improved, regaining his flesh and strength with remarkable rapidity, and on September 12, 1894, physical examination was as follows: In right lumbar region, one inch below the crest of the ilium, is a cicatrix three inches long with a small sinus at either end. Two inches below this cicatrix is another small sinus; four inches further down a third. No dead bone can be detected with a probe, and there is only a slight discharge from the sinus. The inguinal glands on the right side are slightly enlarged, but steadily diminishing in size. There remains no trace of the large tumor already described at the beginning of the treatment, and the general condition of the patient has nearly returned to normal. He now weighs (November 15th), one hundred and forty-eight pounds, a gain of twenty-nine pounds since August, and fully forty pounds since June. He has resumed his occupation as a printer.

I will say that no microscopic section was examined before treatment was begun, but the clinical history and physical examination, verified by a large number of

surgeons of the Surgical Section at the Academy, left no doubt as to the diagnosis. It was an osteo-chondro sarcoma, as several hard cartilaginous masses sloughed out, examination of which showed them to be chondroma. The majority of the tumor was sarcomatous tissue.[1]

CASE III. *Spindle-celled Sarcoma of Scapula with an Extensive Involvement of Chest-wall.*—Sarah C——, aged sixteen, was admitted to the New York Cancer Hospital June 20, 1894. There was no history of malignant disease in the family, and her personal history was good up to four months previous to admission. At that time she first noticed a small tumor in her back, over the left scapula. The tumor rapidly increased in size, and gradually extended, both in front and behind, until it had involved the larger portion of the left thoracic wall. It was associated with constantly increasing pain and interference with the movements of her arm. Physical examination, June 25, 1894, showed the following condition : There was a hard fixed mass involving almost the entire region of the left thorax behind, extending from the clavicle to the lowest rib, vertical measurement being thirteen inches. Horizontally it extended from the median line behind to the middle of the sternum in front, and from one inch below the clavicle seven inches downward, involving a large portion of the region of left breast. The entire tumor was firmly fixed to the chest-wall, but the overlying skin was normal in appearance, and not adherent. The left arm could not be raised to a right angle, and movements forward and backward were correspondingly limited. A portion of the tumor was removed, and microscopical examination proved it to be a spindle-celled sarcoma. In consideration of the rapidity of the growth and enormous extent involved,

[1] Since the paper was read, a portion of the thickened ilium at site of tumor was removed, December 1, 1894, for examination, and no trace of sarcoma could be found on microscopical examination.

I did not believe even temporary arrest possible, nevertheless I decided to try the injections for two or three weeks and watch the effect. To my astonishment, improvement was immediate and very rapid. Within three weeks the arm could be raised to a vertical position, and within one month the growth in front had nearly disappeared. The injections were continued at intervals of from twenty-four to forty-eight hours, and the reactions were never severe enough to keep the patient in bed more than a few hours after the injection. The improvement continued without any interruption until the latter part of October, when no trace of the tumor could be found either in front or behind. The treatment has been discontinued since that time, and the patient is presented this evening without the slightest suspicion of the sarcoma or even any induration visible. She has regained her normal weight and her usual health and strength.

This case is to my mind the most brilliant of the entire series, and must be regarded as the crowning triumph of the toxin treatment. Here we have a tumor, the great malignancy of which was shown by the rapidity of its growth and the extensive involvement that had occurred within four months, and the diagnosis of spindle-celled sarcoma established by the microscopic examination of a skilled pathologist,[1] entirely disappearing within three and a half months from the beginning of the treatment with the mixed toxins.

There are some points of unusual interest in this case. 1. All of the injections were made in one portion of the tumor, over the lower part of the scapula, and within a radius of two inches. 2. There was no breaking down, the tumor disappearing entirely by absorption. 3. Only a single preparation of the toxins was used throughout, viz., mixed cultures of erysipelas streptococci and bacillus prodigiosus, grown together

[1] Dr. G. F. Brooks, Pathologist to Post-Graduate Medical School and Hospital.

in bouillon and sterilized by subjecting them to a temperature of 58° C.

Case IV. *Probable Sarcoma of Sternum.*—The patient, aged thirty-nine, female, was first seen by me in consultation with Dr. Farquhar Ferguson, August 21, 1894. Two of her sisters had suffered from cancer, but she herself had been well up to four months before consulting me. At that time she noticed a small swelling over the upper portion of the sternum. It steadily increased in size, was but slightly painful, and seemed fixed to the sternum. Her general health had become considerably impaired and she had lost weight. Physical examination showed the upper third of the sternum occupied by a tumor three inches in diameter, symmetrical in outline, and firmly connected with the sternum itself. In consistence it was about the same as an ordinary sarcoma when the cellular structure predominates. A few enlarged glands were present along the border of the left pectoral muscle.[1] The injections were begun August 23, 1894, and severe reactions followed the administration of very small doses. The injections were repeated every other day, and at the end of the first week most of the tumor was soft and fluctuating. A small incision was made under cocaine and the broken-down material allowed to escape. The injections were continued in the portions of the tumor still hard for about four weeks longer. At the end of that time it had apparently disappeared, there only remaining two small sinuses at the points where incision had been made to permit the degenerated tumor-tissue to escape.

Her general health has much improved, and although the case is too recent to speak of it as a permanent cure, the results in my earlier cases make it not unreasonable to hope for a cure in this case.[2]

[1] Material drawn with aspirating needle was examined by Dr. Ferguson and he believed it to be sarcoma.

[2] A tumor in the left lumbar region broke down under the injections

Carcinoma.—Of the cases of carcinoma I have only time to mention in detail a single case.

Mrs. W——, aged thirty-four, with a good family and previous personal history, came to the Methodist Episcopal Hospital in July, 1894, with a very rapidly growing epithelioma of the lower jaw, involving the floor of the mouth, under portion of tongue, and all of the soft tissues of the chin. There was an area the size of a silver half-dollar, the site of a typical epitheliomatous ulcer. The tumor had followed quickly an injury to the chin, and this fact in connection with the age of the patient, would have pointed to a diagnosis of sarcoma, had not an examination showed it to be epithelioma.

She was kindly referred to me by Dr. George R. Fowler, and treatment was begun early in July; from three to seven minims of the mixed toxins were injected into soft parts of chin which were involved in the disease. Within two weeks the ulcer had nearly healed, and within three weeks it had entirely healed and the parts almost regained their normal appearance. The floor of the mouth also showed a striking improvement. This improvement unfortunately did not continue more than a few weeks, and then a change for the worse appeared, and the injections no longer seemed to control the disease. A number of other cases of carcinoma, including epithelium, showed striking but only temporary improvement. I have seen very great œdema of the arm, caused by recurrent cancer of the breast, disappear with astonishing rapidity after two or three injections.

My feeling as regards the treatment of carcinoma

in sternal tumor and discharged material that could not be differentiated from that coming from sternal tumor.

Later Note.—January 15, 1895. A recent examination of scrapings from sinuses in sternum and back, by Professor E. K. Dunham, shows that both tumors were probably of tubercular origin. The effect of the toxins is in harmony with the well-known effect of actual erysipelas upon tubercular lesions of skin and glands referred to by Mauriac.

with the toxins has, up to the present time, been very conservative, and until further experiments have been made I should not advocate its general adoption.

The increasing number of well-authenticated cases of carcinoma that have been permanently cured by attacks of accidental erysipelas, as well as the undoubted antagonistic action I have observed in my own cases treated with the toxins, should make us extremely hopeful that, in the near future, some of the success that has been achieved in sarcoma may be extended to carcinoma.

This is not the time nor place to attempt an explanation of this curative action of these germs. It would bring up the whole discussion of the etiology of cancer, a question surrounded by almost innumerable obstacles, and not yet settled to the satisfaction of the majority of the profession. Personally, I believe the evidence at present strongly in favor of the microparasitic theory of the origin of both sarcoma and carcinoma. Accepting this theory, the explanation of the action of toxins on malignant tumors is very easy; on any other theory I believe an explanation impossible.

Results with others who have Tried Toxins in the Way I have Recommended, and Using the Same Preparations.—At the American Surgical Association, at Washington, last May, in the course of the discussion, Dr. Keen stated that he had had no beneficial results in several cases that he had treated with the toxins. In my reply I stated that, up to that time, I had had the greatest difficulty in getting a stable preparation and one that could be relied upon for any length of time. The results that I reported at the time only followed persevering and often prolonged efforts, using many cultures differing greatly in value. It should be remembered that up to that time I had not recommended the general use of the toxins, and only at the request of a few surgeons whom I personally knew, was any sent for trial. It is clearly unfair to allow the results

of a few such imperfect experiments to stand as a test of the value of the treatment.

Fortunately, since that time, with the help of Mr. B. H. Buxton, who has, during the past year, devoted a large portion of his time to investigating this subject, and aiding me in perfecting the preparation, it has been found possible to obtain a preparation of the mixed toxins sufficiently stable to render accurate dosage possible. It is much more effective than any I had hitherto used, due to the increasing virulence of the streptococcus caused by passing it through a series of rabbits.

The method of preparation I will refer to more in detail later, but at present I wish to refer to a few cases to prove that like good results can be obtained from the treatment in other hands than those of its author.

Dr. R. Tilly, of Chicago, in a letter dated August 16th, describes a case of sarcoma of the orbit, which he considered beyond operation, mostly on absolutely unfavorable prognosis. He tried at first the filtered toxins, with little or no benefit. He then used the unfiltered, including the bodies of streptococcus and B. prodigiosus, killed by temperature 58° C. The first three doses had no effect ; the fourth gave a very severe chill and a temperature of 106° F. Within twenty-four hours the temperature was 97° F. The injections were continued about every other day for two or three weeks without much rise of temperature.

The tumor had steadily decreased, and August 16, 1894, it had entirely disappeared. I have not heard of the subsequent history of the case.

Dr. J. Alexander Moore, of Helena, Mont., has used the toxins in four cases. He obtained the preparations from me, and used them as nearly as possible in the way I have advised. His first case was a scirrhous cancer of breast, recurrent. The left lung and liver were involved. He began injections January, 1894. He states that the disease was undoubtedly re-

strained locally for some time, but owing to the advanced stage and generalization the treatment was discontinued.

Case II.—Epithelioma involving entire lower lip, two years' history. Growth ulcerating. Injections for above three weeks failed to produce any decrease in size.

Case III.—January 15, 1894. The patient, aged thirty-one, female. Recurrent, small, round-celled sarcomata of supra-clavicular region. Operation had been done May, 1893. Recurrence in two months followed. Injections with toxins of erysipelas and prodigiosus were begun January 15, 1894, and continued every two or three days until February 15th; at that time the original tumors, several in number, had entirely disappeared, but other new ones appeared.

The patient lived at a distance from town, and the treatment could not be given with regularity. On September 15, 1894, there were five small nodules to be felt at site of former tumors. Dr. Moore writes: "The injections, when prosecuted with vigor, have never failed in this case to reduce or obliterate the tumors." When the nature of these tumors—small round-celled sarcoma, the most malignant type—is considered, the efficacy of the toxins cannot be doubted.

Case IV.—Male, aged thirty-one, tumor, size of a goose egg, attached to right mastoid bone, and not adherent to skin. The lymphatics were enlarged and indurated. The growth had been noticed two months. Treatment was begun April 4, 1894; very good reactions followed. There was some breaking down of tumor. August 20th, the tumor had entirely disappeared. Two small lymphatics could still be felt just above clavicle, but these were gradually becoming smaller. It is true, no microscopic examination was made in this case, but the case had been examined by other physicians of skill and experience.

Dr. Moore writes: "I am quite satisfied as to the effect of inoculation with the toxic products of erysipelas

and B. prodigiosus in sarcoma, but only reasonably so in carcinoma."

Dr. George M. Kreider, of Springfield, Ill., surgeon to St. John's Hospital, writes me that he has used the toxins in three cases. The preparation used was the unfiltered, sterilized by 58° C., prepared by Mr. Buxton, the same as used by myself in the case reported.

One case was an inoperable sarcoma of the ilium of unusual size, involving not only the ilium but surrounding tissues. He writes that the result was very striking, but owing to the prostration of the patient he was obliged to stop the treatment. "Two hundred grammes (6¼ ounces) sloughed out, and it would seem certain that, had treatment been undertaken sooner, he would have recovered."

"The other cases of cancer have made gratifying progress, notably one case of uterine cancer. She was bedridden because of the swelling of the right leg and foot. The swelling disappeared entirely in three weeks, and has not returned, although the patient is on her feet continually. The pains and bleeding have also disappeared."

Dr. Thomas F. Rumbold, of San Francisco, has tried the toxins in a patient suffering from recurrent round-celled sarcoma, with the following result: In June, 1892, a tumor the size of a hickory-nut was noticed from the right breast. On July 7, 1892, it was removed and pronounced non-malignant, but within a few weeks it returned; a second operation was performed, taking off most of the breast. Within six months a third and fourth operations were performed, removing the whole of the breast but not the axillary glands. In July, 1893, the tumor again recurred. A very thorough operation was then made by Drs. Lane and Plummer, of San Francisco, and the axillary glands, which were then involved, were removed. A microscopic examination showed the tumor to be round-celled sarcoma. Since then three other operations, making eight in all, were performed.

The sarcoma again recurred and was growing rapidly, when early in August, 1894, Dr. Rumbold wrote me requesting me to send him some of the toxins. The first injection was made August 14, 1894.

In a letter dated September 12th he says : " I am very glad to inform you that the case has progressed very favorably ; in fact, the treatment has been a marvel in all respects to everyone who has seen the case. She is visited twice a week by a number of the most prominent physicians, who are greatly interested in the case and treatment. I do not think there is one-eighth of the tumor left, and I believe she would recover entirely without another injection ; but, to make matters sure, I will continue the injections, as suggested in your letter."

A later letter states that the tumor had entirely disappeared. The patient was considerably weakened by the treatment and was suffering from persistent nausea.

Time will permit me to refer to only one other case outside of those of my own personal cases ; but this case is too important to leave unnoticed. As the case was reported in full at the last meeting [1] of the Throat Section at the Academy, I need only give a very brief summary of the facts :

The patient was a boy, aged sixteen, with a very large spindle-celled sarcoma of the palate and pharynx. He was a patient of Dr. Walter B. Johnson, surgeon to Paterson General Hospital, of Paterson, N. J., and I was asked to see the case in consultation, in October, 1893. The physical examination at that time, made by Dr. Johnson, showed a tumor involving the entire soft palate, pillars of the fauces, region of the tonsils, and extending forward over the hard palate to within a half-inch of the incisor teeth, backward and downward, involving a portion of the pharyngeal wall, the whole base of the tongue, the epiglottis, and upper part of the larynx, but not extending to the true vocal cords.

[1] Medical Record, November 17, 1894.

The infected parts were thoroughly impregnated with sarcomatous deposit, and the soft palate was increased to about three times its normal thickness. The growth consisted of cauliflower-like granulations, varying in size from a kernel of rice to a pea. The uvula was entirely destroyed; the cervical glands were enlarged. The patient had lost considerable flesh and strength, but was not cachectic. His weight was 86 pounds. He had difficulty in deglutition, and could not breathe through his nose. A microscopical examination made by Dr. James W. Williams showed the growth to be spindle-celled sarcoma. The tumor was so extensive that I expressed very little hope of any permanent benefit being derived from the toxins, but advised giving the treatment a short trial.

Dr. Johnson began, October 31, 1893, and continued the injections with occasional intervals for seven months. The reaction temperature following the injection varied between 99° and 103° F. The preparation used was the filtered toxins, grown separately and kept in separate bottles, mixing them at the time of injection. I had not then begun growing them together.

The result of the treatment is a constant, slow improvement, some of the sarcomatous tissue undergoing necrobiosis, some disappearing by absorption. In October, 1894, the patient weighed 107 pounds. He had had no treatment for three months, and the tumor had apparently entirely disappeared. (Two days ago Dr. Johnson wrote that there was one point in the mouth that looked slightly suspicious, and he decided to resume treatment for a short time. This same thing occurred once before, and quickly disappeared when the injections were begun.)

Since the reading of the paper another successful case has been reported to me by letter, and its great importance warrants inserting it here. The case was a patient of Dr. Judson C. Smith, of New York, Director of the Laboratory of the Post-Graduate Medical School

and Hospital, and was treated by him personally. He writes : " You may refer to my case of sarcoma treated with the toxins as follows :

" Mrs. W——, aged twenty-eight, good family and personal history. Tumor of right side of neck about the size of an orange ; had been growing one year. September 1st, when she came under my care, she was extremely emaciated, anæmic, and scarcely able to leave her bed. The tumor was beginning to break down, and the patient was septic, having a temperature of 103° F. She also had dropsy of lower limbs.

" On September 11, 1894, I made an incision under ether and scraped out a large mass of the tumor, but owing to the patient's poor condition no attempt was made to remove the whole mass, which was deeply seated, extending beneath the clavicle. The wound was packed with gauze, and four days later I began the injection of erysipelas and prodigiosus toxins. These were continued eight weeks. She has no sign of tumor now, has gained twenty-five pounds in weight, and appears perfectly well. Microscopic examination proves the growth to be small round-celled sarcoma."

These results in the hands of independent observers are sufficient, I think, to confirm my own conclusions as to the value of the toxins in sarcoma.[1]

As to the question whether or not the toxins should be tried in all cases of inoperable sarcoma, there are many things to be considered. In the hands of men of experience, and very carefully administered, I believe the treatment to be attended with but little if any risk. My results show what may be accomplished in apparently the most hopeless cases ; hence the importance, if possible, of giving such cases the benefit of a trial. If improvement is likely to occur, my experience has

[1] Since the paper went to press several additional successes in sarcoma in the hands of other surgeons have been reported to me by letter.

been that some evidence will present itself within two weeks after beginning the injections. It must be remembered that we have to deal with a very powerful, and as yet not thoroughly understood, agent, and it should be used with the greatest caution. Individuals vary greatly in their susceptibility to its action, and the minimum dose should be used at first. I have myself never had a death from it, though in one case I think the end was probably hastened. This was an enormous sarcoma of the scapula, involving clavicle, chest-wall, and a large portion of the humerus. The patient was very weak and emaciated, and the treatment should never have been attempted in a case so far gone. Only a single dose and a very small one (two minims) was given, the patient gradually grew weaker, and died four days later.

I will merely refer to another field for the use of the toxins, and one that seems to me likely to be very important, viz.: After primary operation for sarcoma, before recurrence has been allowed time to take place, the reasons for using the treatment in such cases are theoretically strong. If, as we have demonstrated, the toxins are able to destroy a large recurrent tumor, there is reason to believe their action would be more certain and effective in destroying the few and invisible germs of the disease left behind after operation. Since at least seventy-five per cent. of the cases do recur after primary operation, the importance of this field is apparent.

Method of Preparation of the Toxins.—To make the toxins of erysipelas and prodigiosus, ordinary peptonized bouillon is put into small flasks, containing 50 to 100 c.c., which, after proper sterilization, are inoculated with the streptococci of erysipelas and allowed to grow for three weeks at a temperature of 30° to 35° C. The flasks are then inoculated with B. prodigiosus, and the cultures allowed to grow for another ten or twelve days at room temperature. At the end of that time, after

being well shaken up, the cultures are poured into sterilized glass-stoppered one-half ounce bottles, and heated to a temperature of 50° to 60° C. for an hour ; sufficient to render them perfectly sterile. After cooling, a little powdered thymol is added as a preservative, and the toxins are ready for use. The toxins when prepared in this way are very much stronger than when filtered through a Pasteur, Chamberland, or Kitasato filter, the active principles contained in the germs themselves being preserved. If, as is sometimes the case, the preparation is found to be too strong to use with safety, it can be diluted with glycerine or sterilized water.

The best method of making the bouillon is to soak a pound of chopped lean meat overnight in water. In the morning strain it through a cloth, make up to 1,000 c.c., and boil for one hour. Then filter through a cloth, add peptone and salt, neutralize and boil again for an hour. The bouillon will then pass through filter-paper perfectly clear, and be ready to put into the flasks. It is not, however, necessary to neutralize the bouillon, as the streptococci will grow even more readily in acid bouillon, and the resulting preparation is, if anything, stronger than when neutralized bouillon is used.

In order to keep up the virulence of the cultures they are put through rabbits in the following way : The hair of the ear is clipped close with a pair of scissors, and the skin washed with weak carbolic acid, and then sterilized water. A minute quantity of a bouillon culture, forty-eight hours old, is then injected subcutaneously in four or five different places in the ear. Forty-eight hours later, after again washing the ear with carbolic acid and sterilized water, a flat needle sterilized in the flame is inserted under the skin at or near a point of inoculation, and the layer of the skin cut off with a sharp sterilized scalpel. The piece of skin is then rubbed well over the surface of an agar tube with a

thick platinum-wire needle. After twenty-four hours in the incubator the colonies of streptococci will show as minute white specks, and from them a pure culture can be obtained. If the agar is made with seventy-five per cent. of bouillon and twenty-five per cent. of urine the streptococci will grow more freely than if bouillon alone is used. For the above brief but clear description of that preparation of the toxins, that up to the present time has proved most efficacious, I am indebted to Mr. B. H. Buxton. The dose of this preparation varies from one to eight minims ; I have had a temperature of 105° F. follow the injection of two minims. I usually begin with the minimum dose and gradually increase until the desired reaction, *e.g*, temperature 103° to 104° F. is reached.

In concluding, I wish to briefly summarize my cases thus far treated. Up to May 31, 1894, I had treated with mixed toxins twenty-five cases of inoperable sarcoma, eight of inoperable carcinoma, and three of sarcoma or carcinoma. In the cases of carcinoma I had had marked improvement in a number of cases, but no cures. The cases were all very advanced recurrent tumors. In sarcoma I stated that there were six cases in which I considered there was a reasonable hope of permanent cure. Six months have passed since then, and none of the six cases have shown any recurrence. Of two other cases which were merely mentioned among the tabulated cases as improving, one has gone on to entire disappearance of the very large tumor and promises to be a cure, and the other, a six-times-recurrent sarcoma of hand, is in perfect health at present, nearly two years since the beginning of the treatment. Since May 31, 1894, I have treated twenty-four cases of malignant tumors, all inoperable and mostly recurrent, with the mixed toxins. Of these cases thirteen were sarcoma and eleven carcinoma. In many of the cases of carcinoma the injections had an undoubted retarding influence, and in some of the cases the improve-

ment was extraordinary, but in no case did the tumor entirely disappear. In the sarcoma cases the effect was far more marked, and although in a number of the cases the disease was so far advanced that there could be no possible hope of recovery, still the powerful controlling influence of the toxins was demonstrated, and had the patient's general condition permitted a prolonged use of the injections, the result might have been otherwise.

In three of the thirteen cases the sarcomas have entirely disappeared, and although no great length of time has elapsed, the results in my older cases make it improbable that relapse will occur. Of my total of thirty-eight cases of inoperable sarcoma, therefore, nine cases promise to be permanently successful. These can be briefly epitomized as follows :

Case I.—A twice recurrent inoperable sarcoma of the neck, with secondary growth, size of an egg, in tonsil. General condition extremely bad ; given by Dr. W. T. Bull three or four months to live. Treatment with erysipelas (living cultures) began May 2, 1891. No treatment since October, 1891. Result : Tumor of neck practically disappeared. Tonsil tumor greatly decreased in size, and has still further diminished the past year. The patient regained his general health in a few months, and November 12, 1894, three and one-half years later, remains in good health.

Case II. *A Large Recurrent Sarcoma of Back and Groin.*—Treated at first with living cultures, later with mixed toxins. No recurrence twenty months after cessation of treatment ; and nearly three years since beginning. (This case I have had the pleasure of showing you this evening.)

Case III. *Large Inoperable Sarcoma of Abdominal Wall and Pelvis.*—Treatment begun February, 1893. Result : Almost entire disappearance in two months. Patient has been in perfect health ever since, with no tendency to relapse twenty-two months later. (Exhibited at Academy of Medicine, November 15, 1894.)

CASE IV. *Large Inoperable Sarcoma of Iliac Fossa.*—Almost entire disappearance of tumor. Treatment begun June, 1893. In good health August, 1894.

CASE V. *Large Inoperable Sarcoma of the Abdominal Wall.*—(Exploratory operation by Dr. Maurice H. Richardson, of Boston. Microscopical examination by Professor Whitney, of Harvard Medical School.) Entire disappearance of tumor under two and one-half months' treatment. In perfect health, December 22, 1894, without trace of recurrence fourteen months after beginning of treatment.

CASE VI. *Recurrent Sarcoma of Leg.*—(Dr. Bull's case.) Treated at the New York Hospital; later at the New York Cancer Hospital. Entire disappearance of tumor. No recurrence December 22, 1894, nearly one year later. (Exhibited at Academy of Medicine, November 15, 1894.)

CASE VII. *Enormous Osteo-chondro Sarcoma of Ilium.*—(Dr. Shrady's case.) Treated at St. Francis and New York Cancer Hospital. Treatment begun March, 1894. Entire disappearance. No relapse December 22, 1894. (Since the reading of paper a portion of thickened tissue at site of old tumor was removed for examination, and no sarcomatous elements were present.) (Exhibited at Surgical Section of Academy, October 12, 1894.)

CASE VIII. *Sarcoma of Hand, Six Times Recurrent.*—Growing rapidly February, 1893, when treatment was begun. Held in check eighteen months. Degenerated tumor tissue removed July, 1894. Patient has since gained twenty pounds, and is in perfect health without relapse December, 1894.

CASE IX. *Sarcoma of Scapula and Chest-wall, Involving Larger Portion of Entire Left Half of Thoracic Wall.*—Entire disappearance in three and one-half months' treatment. In perfect health at present (January 13th), two months since treatment was discontinued. (Exhibited at Academy, November 15, 1894.)

With exception of the first, all of these cases were treated with the mixed toxins of erysipelas and bacillus prodigiosus, the streptococcus cultures having been obtained from a fatal case of erysipelas. That the bacillus prodigiosus plays a very important part in the action of the toxins on sarcoma, I have not only repeatedly demonstrated, by using the two singly and combined, but my conclusions have been verified by others. The prodigiosus toxins used alone have a marked effect in causing degeneration and absorption of sarcomatous tissues, but the combined action of the two toxins is greater than when either is used alone. I have also found by experiment that sarcina used with erysipelas has a similar effect.

When we consider that all of the cases reported were hopeless, not only from an operative stand-point, but from any hitherto known method of treatment, that in every case the diagnosis was established according to the most approved principles of medical science, confirmed clinically by the most eminent surgeons, and microscopically by leading pathologists, we are in a position to understand the importance of this subject.

I cannot sufficiently express my indebtedness to Dr. Alexander Lambert and Mr. B. H. Buxton for invaluable bacteriological assistance, and it is largely due to their most careful and skilful work that the preparation of the toxins has been so far perfected as to make accurate dosage possible.

NOTE.—By an unfortunate mistake the photographs illustrating the cases were omitted.